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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/527,950	09/30/2005	Timothy P. Tully	2826.1000-005	1059

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EXAMINER	
DUTT, ADITI	

ART UNIT	PAPER NUMBER
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/527,950	TULLY ET AL.	
	Examiner	Art Unit	
	Aditi Dutt	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *17-18,19l-19o,25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16,19a-19k,20-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 March 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/3/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

1. The amendment of 18 February 2008 has been entered in full.

Election/Restrictions

2. Applicant's election with traverse of Group I, claims 1-11, 19(a-k), 20-25 in the reply filed on 18 February 2008 is acknowledged.

3. The traversal is on the ground(s) that the methods in the inventive Groups are all related by their involvement with candidate compounds for enhancing CREB-dependent actions and effects, therefore, a search of all the Groups would not pose an undue burden on the Office. This is found to be persuasive in part because claims 12-16 are broadly interpreted by Examiner to read upon the method of Group I, i.e. identifying candidate compounds that enhance the CREB pathway function using an in vitro screening method. The restriction requirement is, therefore, withdrawn with respect to claims 12-16 (Group II) that are rejoined and will be examined along with the claims of Group I in the current application.

4. However, claims 17-18, 19(l-o) and 25 recite the special technical feature of assessing the in vivo effect on long term memory formation in an animal, which is not required by the in vitro methods of the other claims. Furthermore, the analytical methods of Group III and Group I/Group II have a special technical feature and are restricted properly, as they are practiced with materially different

process steps for materially different purposes and each requires a non-coextensive search because of different starting materials, process steps, and goals. Furthermore the classification is different, and the subject matter is divergent, therefore, would result in an undue search burden on the Examiner. Additionally, claim 25 was mistakenly included in Group I in the last Office Action, since the limitation "animal" depends from claim 19(l-o) of Group III, and reads upon in vivo treatment. Examiner apologizes for the error and requests the inclusion of claim 25 in Group III.

5. **The requirement is still deemed proper and is therefore made FINAL.**

6. Claims 17-18, 19(l-o) and 25 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 18 February 2008.

7. Group I, claim(s) 1-16, 19(a-k), 20-24, drawn to a method of identifying candidate compounds for enhancing CREB pathway function and assessing the effect on CREB-dependent gene expression, are being considered for examination in the instant application.

Claim Objection

8. Claims 1, 2, 5, 7, 8, 11-13, 16, 19 and 23 are objected to because of the following informalities:

(i) Claim 19(l-o) is objected for reciting a non-elected invention.

(ii) Claims 1, 2, 5, 7, 8, 11-13, 16, 19 and 23 recite the acronyms "CREB" and "CRE", which should be spelled out in all independent claims for clarity. Appropriate correction is required.

Claim Rejections - 35 USC § 112-Second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1, 2, 7, 8, 13 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claims 1 and 19 recite the limitation "suboptimal dose". The term "suboptimal dose" is not defined by the claim, the specification does not provide a standard for ascertaining the appropriate concentration of the CREB stimulating agent to attain a suboptimal dose, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Although the instant specification describes "suboptimal dose" as that amount yielding a "50% or less maximal indicator activity" that is above natural celllular fluctuations, it is vague and unclear. For example, it is not clear as to what 'cellular fuctuations' are considered, or what is 'maximal indicator activity', etc.

11. Claims 2, 8 and 13 recite the limitation "contacted with said test/candidate compound prior to contact with said CREB function stimulating agent" (emphasis

added). There is insufficient antecedent basis for this limitation in the claims because claims 1a, 7g, and 12a, recite contacting host cells/cells of neural origin with "a test/candidate compound and with a suboptimal dose of a CREB function stimulating agent", i.e. claims 1, 7 and 12 are interpreted such that both (test/candidate compound and CREB function stimulating agent) are added together. Clarification is particularly required because the instant specification does not provide a criticality of this limitation (see page 22, lines 1-2).

12. Claim 7(g) recites the limitation "cells of neural origin are different from the host cells of step a)". It is unclear as to what aspect of the difference is being referred to, since the host cell and the cells of claim 7 are of neural origin (e.g. neuroblastoma). Is the limitation referring to the cell type (e.g. from a different nucleus of the brain)? Appropriate clarification is required.

Claim Rejections - 35 USC § 112-Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1-4, 6-10, 19(a-k), 20-22 and 24, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for identifying a candidate compound for enhancing cyclic AMP response element binding protein (CREB) pathway function by contacting host cells/cells of neural origin with a test compound (e.g. NPY) and forskolin and comparing the

indicator activity or CREB dependent gene expression with control cells, does not reasonably provide enablement for the identification of a candidate compound following the same steps by using any CREB function stimulating agent in suboptimal amounts in combination with any test agent. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

14. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, include the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. The instant disclosure fails to meet the enablement requirement for the following reasons:

15. The claims are directed to a method of identifying candidate compounds for enhancing CREB pathway function, (i) by contacting host cells comprising an indicator gene linked to a CRE promoter with a test compound and CREB function stimulating agent; (ii) determining the indicator activity and comparing the same in the above cells versus control cells contacted with the CREB function stimulating agent but not the test agent; (iii) selecting the test compound if the indicator activity in cells treated with CREB function stimulating agent but not the test agent is increased relative to the above control cells; (iv) selecting

the test compound if the indicator activity in control cells not treated with the CREB function stimulating agent but with the test agent is not significantly different from the activity elicited by control cells treated neither with the test agent nor with the CREB function stimulating agent; (v) repeating the above steps with a range of concentrations of the test agent; wherein the host cells are neuroblastoma cells, and the indicator gene is luciferase (claims 1, 3-4, 6). The claims further recite identifying and confirming the candidate compound by assessing the effect on CREB-dependent gene expression by contacting cells of neural origin with the candidate compound and CREB function stimulating agent, assessing and comparing the difference in the endogenous CREB dependent gene expression in the above cells versus that observed in control cells that have been contacted with the CREB function stimulating agent but not with the candidate compound, wherein the cells are hippocampal neurons and the CREB function stimulating agent is forskolin (claim 5, 7, 9-12, 14-16).

16. The specification of the instant application teaches that the CREB transcription factor plays a major role in the formation of long term memory and long term synaptic plasticity (page 10, lines 21-22). The specification also teaches that the CREB pathway function denotes a variety of activities, such as DNA binding ability, phosphorylation, ... etc. (page 14, lines 9-24). The specification further teaches high throughput cell-based assays comprising primary, secondary and tertiary screens for identifying cognitive enhancers that act by increasing CREB pathway function, wherein the cognitive enhancers do

not have any effect on CREB pathway function alone, however, enhance the activity in combination with a CREB stimulating agent (page 2, lines 8-12). The instant specification lists a vast array of CREB stimulating agents comprising drugs, chemical compounds, co-factors, saccharides, genes, ... etc (page 17, lines 18-31; page 18, lines 1-5). However, the specification does not teach any methods or working examples to indicate that all CREB function stimulating agents will effectively function at a suboptimal dose, with all test agents to enhance CREB pathway function. Undue experimentation would be required of a skilled artisan to determine such.

17. Relevant literature teaches that CREB plays a critical role in several functions, like long term memory in mice, dendritic spine formation in hippocampal neurons, neurite outgrowth in PC12 cells. The art further teaches that CREB is regulated by multiple factors producing "diverse stimuli" that "can result in divergent cell fates" (Pugazhenthi et al. JBC 274: 2829-2837, 1999; Discussion, page 2834-2835, para 2-3). However, the art does not provide any information with regards to the use of any CREB function stimulating agent with any test agent in assays for identifying a candidate compound for increasing CREB function. On the contrary the teachings in the art prove otherwise. For example, NPY augmented forskolin stimulated luciferase activity, but did not affect the thapsigargin (a modulator of intracellular calcium concentration and a CREB function stimulating agent as described in the instant specification – page 17, lines 26-27) induced activity significantly (Sheriff et al. Reg Pept 75-76: 309-

318, 1998; abstract; Figure 5). Sheriff et al further explain that thapsigargin depletes intracellular calcium stores, thereby preventing NPY which acts on the reporter gene via intracellular calcium to exert an enhanced effect. In addition, the instant specification teaches that the "suboptimal dose of CREB stimulating agent is determined empirically and will vary depending upon a variety of factors, including the pharmacodynamic characteristics of the particular CREB function stimulating agent and the particular cells to be contacted" (page 20, lines 1-4), thereby implying the potential variability and unpredictability in obtaining successful results. This explains that each test agent will have a different mechanism of action, therefore, to combine all or any CREB stimulatory agents with any test agent will result in undue experimentation for a skilled artisan. In the absence of guidance regarding the use of any CREB function stimulating agent at a suboptimal dose in combination with any test agent, for identifying a candidate compound that will enhance CREB function with a reasonable amount of success, undue experimentation would be required of a skilled artisan. The specification must provide such guidance commensurate in scope with the claims. The specification's general discussion of a broad range of CREB stimulating agents constitutes an invitation to experiment by trial and error.

18. Due to the large quantity of experimentation necessary to identify a candidate compound for enhancing CREB pathway function by combining any CREB function stimulating agent at a suboptimal dose with a test compound, the lack of direction/guidance presented in the specification; the absence of working

examples directed to same; the complex nature of the invention; the unpredictability of the ability of all test compounds to effectively enhance the activity induced by any CREB function stimulating agent; and the breadth of the claims which fail to recite specific CREB function stimulating agent, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

Claim Rejections - 35 USC § 103

19. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

20. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

21. Claims 1, 3-7, 9-12, 14, and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sheriff et al., (Reg Pept 75-76: 309-318, 1998), in view of Herzog et al. (PNAS 89: 5794-5798, 1992).

22. The claims are directed to a method of identifying candidate compounds for enhancing CREB pathway function, (i) by contacting host cells comprising an indicator gene linked to a CRE promoter with a test compound and CREB function stimulating agent; (ii) determining the indicator activity and comparing the same in the above cells versus control cells contacted with the CREB function stimulating agent but not the test agent; (iii) selecting the test compound if the indicator activity in cells treated with CREB function stimulating agent but not the test agent is increased relative to the above control cells; (iv) selecting the test compound if the indicator activity in control cells not treated with the CREB function stimulating agent but with the test agent is not significantly different from the activity elicited by control cells neither treated with the test agent nor with the CREB function stimulating agent; (v) repeating the above steps with a range of concentrations of the test agent; wherein the host cells are neuroblastoma cell, and the indicator gene is luciferase (claims 1, 3-4, 6). The claims further recite identifying and confirming the candidate compound by assessing the effect on CREB-dependent gene expression by contacting cells of neural origin with the candidate compound and CREB function stimulating agent, assessing and comparing the difference in the endogenous CREB dependent gene expression in the above cells versus that observed in control cells that have

been contacted with the CREB function stimulating agent but not with the candidate compound, wherein the cells are hippocampal neurons (claim 7, 9, 10, 12, 14, 15). Furthermore, the claims recite that the CREB function stimulating agent is forskolin (claims 5, 11, 16).

Range of concentration:

23. Sheriff et al. teach a method to determine the neuropeptide Y or NPY induced effect on CREB pathway function, such as CREB phosphorylation and CaM kinase activity. Sheriff et al. specifically teach the transfection of cells from the neuroblastoma cell line SK-N-BE2 with a fusion gene containing the CRE site linked to firefly luciferase (indicator) gene. The reference further teaches that the treatment of the transfected cells with NPY and forskolin results in a significant increase of luciferase activity as compared to control cells treated with forskolin but not with the NPY (Abstract; Results: Section 3.5; Figure 5, 5^{th} and 6^{th} bar). Furthermore, Sheriff et al. demonstrate that the luciferase activity in control cells treated with NPY but not with forskolin is not significantly different from the activity elicited by control cells that are not treated with either forskolin or with NPY (Figure 5, 1^{st} and 2^{nd} bar).

24. Sheriff et al. do not teach repeating the method steps with a range of concentrations of the compound or NPY.

25. However, since the disclosure does not specify criticality of the claimed range of doses, optimization within prior art conditions or through routine experimentation is obvious to one skilled in the art.

As stated in MPEP 2144.05:

"The differences in concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." "The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages". *In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955); Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382; Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 UDPQ2d 1843 (Fed. Cir.).*

26. It would have been, therefore, obvious to the person of ordinary skill in the art at the time the claimed invention was made to determine the optimal range of doses of the test compound to be added to neuroblastoma cells for identifying compounds such as NPY that enhance the CREB pathway function, as taught by Sheriff et al. The person of ordinary skill in the art would have been motivated to perform such tests to assess the optimum dose of NPY required for augmenting forskolin induced effect on CREB pathway function, because NPY is known to exert several biological functions in the central and peripheral nervous system through induction of CRE binding activity in the hypothalamus. The person of ordinary skill in the art would have expected success because the method assessing in vitro activity of regulatory peptides as a part of screening for candidate compounds was being experimented and performed in the scientific and medical community, at the time the invention was made.

Gene Expression:

27. Sheriff et al. teach also teach contacting cells (not transfected) of the neuroblastoma cell line with NPY and forskolin, and assess the expression of

endogenous gene containing CRE (Y1 receptor). The reference further teaches that although NPY treatment increases the Y1 mRNA expression, forskolin was more potent in upregulating Y1 receptor message, when compared to untreated controls (page 314, Section 3.6 of Results; Figure 6).

28. Sheriff et al. also do not teach the addition of both NPY and forskolin to neuroblastoma cells. However, in the absence of unexpected results, it would have been prima facie obvious to one of ordinary skill in the art to combine the teachings of the reference and to treat the cells with both NPY (as the candidate compound) and forskolin. Each of these compounds had been taught by the prior art to augment CREB dependent gene expression and increase Y1 mRNA. The instant situation is amenable to the type of analysis set forth in *In re Kerkhoven,205 USPQ 1069 (CCPA 1980)* wherein the court held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to for a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant process claims, given the teaching of the prior art of processes wherein the Y1 gene expression is enhanced by NPY and by forskolin individually, it would have been obvious to contact cells with both NPY and forskolin because the idea of doing so would have logically followed from their having been individually taught in the prior art to be useful as compounds for the same purpose of enhancing CREB dependent gene expression. One of ordinary

skill in the art would have reasonably expected to enhance Y1 gene expression upon treating cells with either or both of these compounds since both had been demonstrated in the prior art to elicit the same result.

Hippocampal neurons:

29. Sheriff et al. do not teach contacting cells that are *hippocampal neurons*. However, Herzog et al teach that the Y1 receptor gene was cloned from a cDNA library derived from the human adult hippocampus (Materials and Methods, para 2, page 5794). As neuroblastoma, hippocampus comprise cells of neural origin comprising neurons and absent evidence to the contrary, contacting of NPY and forskolin to upregulate Y1 gene expression in *hippocampal neurons* would be obvious to one skilled in the art in view of Sheriff et al., and Herzog et al. Furthermore, in considering the disclosure of a reference, it is proper to take into account not only specific teaching of the reference but also the inferences which one skilled in the art would be reasonably be expected to draw therefrom (*In re Preda*, 401 F.2d 825, 159 USPQ 342, 344 (CCPA 1968)). Also, a reference must be considered, under 35 U.S.C. 103, not only for what it expressly teaches but also for what it fairly suggests; all disclosures of prior art, including unpreferred embodiments, must be considered in determining obviousness (*In re Burckel* 201 USPQ 67 (CCPA 1979)).

30. It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the method for elevating Y1 message in neuroblastoma cells as taught by Sheriff et al., by using *hippocampal neurons*.

The person of ordinary skill in the art would have been motivated to make that modification and would have expected success because Y1 is present in the hippocampus as demonstrated by Herzog et al. Therefore, the claimed invention as a whole was clearly *prima facie* obvious over the prior art.

31. Claims 19(a-k) and 20-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sheriff et al., (Reg Pept 75-76: 309-318, 1998), in view of Herzog et al. (PNAS 89: 5794-5798, 1992), and further in view of Barad et al. (PNAS 95: 15020-15025, 1998).

32. The claims are directed to a method of identifying candidate compounds for enhancing CREB pathway function, (i) by contacting host cells comprising an indicator gene linked to a CRE promoter with a test compound and CREB function stimulating agent; (ii) determining the indicator activity and comparing the same in the above cells versus control cells contacted with the CREB function stimulating agent but not the test agent; (iii) selecting the test compound if the indicator activity in cells treated with CREB function stimulating agent but not the test agent is increased relative to the above control cells; (iv) selecting the test compound if the indicator activity in control cells not treated with the CREB function stimulating agent but with the test agent is not significantly different from the activity elicited by control cells neither treated with the test agent nor with the CREB function stimulating agent; (v) repeating the above steps with a range of concentrations of the test agent; wherein the host cells are

neuroblastoma cells, the CREB function stimulating agent is forskolin and the indicator gene is luciferase. The claims further recite identifying and confirming the candidate compound by assessing the effect on CREB-dependent gene expression by contacting hippocampal cells with the candidate compound and CREB function stimulating agent, assessing and comparing the difference in the endogenous CREB dependent gene expression in the above cells versus that observed in control cells that have been contacted with the CREB function stimulating agent but not with the candidate compound, wherein the compound is selected if the gene expression in the above treated cells is increased relative to control groups matching treatment criteria as in (ii), (iii) and (iv).

33. The teachings of Sheriff et al. and Herzog et al are set forth above.

34. Sheriff et al. and Herzog et al. do not teach changes in gene expression after the addition of both forskolin and test agent/candidate compound to the hippocampal neurons.

35. Barad et al., teach a method of elevating cAMP concentrations, using hippocampal slices from mice, that were incubated with increasing range of 4 concentrations of the phosphodiesterase type IV inhibitor, rolipram (0, 0.03, 0.3 and 3 μM) in the presence or absence of the adenylyl cyclase activator forskolin (abstract, page 15021). The reference also demonstrates that cAMP levels at lower concentrations of rolipram (up to 0.3 uM) were not significantly different from the basal level (without rolipram and forskolin) (page 15021, 'results' para 1, Figure 1). Furthermore, the results demonstrate that the endogenous cAMP

levels in cells contacted with rolipram and forskolin are increased relative to the levels in the control group treated with forskolin but not rolipram. It is noted that forskolin is an adenylyl cyclase activator as stated above, which would inherently increase endogenous cAMP concentrations via increased adenylyl cyclase expression as evidenced by Insel et al (Cell Mol Neurobiol 23: 305-314, 2003, abstract). It is also well known that adenylyl cyclase is a positive effector of CREB, inducing CREB dependent gene expression.

36. As already explained above, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the method for elevating Y1 message in neuroblastoma cells as taught by Sheriff et al., by using *hippocampal neurons*. It would, therefore, have also been obvious to the person of ordinary skill in the art at the time the invention was made to modify the method for elevating Y1 message in neuroblastoma cells as taught by Sheriff et al., by elevating cAMP levels from hippocampal slices as taught by Barad et al. The person of ordinary skill in the art would have been motivated to substitute hippocampal neurons for hippocampal slices, because neurons are individual cells that would elicit the CREB dependent gene expression in a cell specific manner. The person of ordinary skill would make that modification with a reasonable expectation of success, because gene expression studies using individual neurons were well established at the time of filing of the instant invention.

37. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

38. Claims 2, 8 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sheriff et al., (Reg Pept 75-76: 309-318, 1998), in view of Herzog et al. (PNAS 89: 5794-5798, 1992), and further in view of Barad et al. (PNAS 95: 15020-15025, 1998).

39. The claims recite that the host cells or the cells of neural origin are contacted with the test/candidate compound prior to contact with the CREB function stimulating agent.

40. The teachings of Sheriff et al., Herzog et al. and Barad et al. are set forth above.

41. Sheriff et al., Herzog et al. and Barad et al. do not teach that the cells are contacted with the compound before contacting the CREB stimulating agent.

42. However, since the disclosure does not specify criticality of the claimed sequence of addition of the test/candidate compound and the CREB function stimulating agent, optimization within prior art conditions or through routine experimentation is obvious to one skilled in the art.

43. It would have been, therefore, obvious to the person of ordinary skill in the art at the time the claimed invention was made to determine the sequential addition of compounds to be added to neuroblastoma cells or hippocamal cells for identifying compounds that enhance the CREB pathway function, as taught by

Sheriff et al., or Barad et al. The person of ordinary skill in the art would have been motivated to perform such tests, to assess the optimum conditions to achieve the desirable increase in CREB function. The person of ordinary skill in the art would have expected success because in vitro cell based assays using one or more agents were routinely performed in the scientific and medical community, at the time the invention was made.

44. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Conclusion

45. No claims are allowed.

46. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

Tully et al. Nature Rev Drug Discovery 2: 267-276, 2003.
(Publication showing instant invention).

Ji et al. Neurobiol Dis 8: 1-10, 2001
(Reference demonstrates the phosphorylation of CREB by kinases in hippocampal neurons and indicates the importance of CREB mediated signaling in memory formation).

47. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aditi Dutt whose telephone number is (571)

272-9037. The examiner can normally be reached on Monday through Friday, 9:00 a.m. to 5:00 p.m.

48. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

49. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov/. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AD
9 April 2008

/Jeffrey Stucker/

Supervisory Patent Examiner, Art Unit 1648